

**Experiment Number:** K06898  
**Route:** Gavage, IV  
**Species/Strain:** Rats/Fischer 344

**Toxicokinetics Data Summary**  
**Compound:** alpha-Thujone/ **Analyte:** alpha-Thujone  
**CAS Number:** 546-80-5

**Request Date:** 7/11/2023  
**Request Time:** 10:03:16  
**Lab:** Battelle Columbus

**Male**

**Treatment Group (mg/kg)**

**1.6 IV Plasma<sup>d</sup>**

**25 Gavage Plasma<sup>b,e</sup>**

**50 Gavage Plasma<sup>c,e</sup>**

C_0min_pred (ng/mL)	684 ± 80		
Cmax_pred (ng/mL)		292 ± 39	955 ± 215
Tmax_pred (minute)		22.4 ± 5.0	23.3 ± 8.5
Cmax_obs (ng/g)		345 ± 110	963 ± 1000
Tmax_obs (minute)		10.0 ± 0.0	5.00 ± 0.00
Alpha Half-life (minute)	8.82 ± 1.07		
Beta Half-life (minute)	201 ± 12		
k01 (minute <sup>-1</sup> )		0.171 ± 0.053	0.150 ± 0.078
K01 Half-life (minute)		4.06 ± 1.27	4.62 ± 2.40
k10 (minute <sup>-1</sup> )	0.0278 ± 0.0029	0.00407 ± 0.00044	0.00517 ± 0.00076
k10 Half-life (minute)	24.9 ± 2.6	170 ± 18	134 ± 20
k12 (minute <sup>-1</sup> )	0.0445 ± 0.0067		
k21 (minute <sup>-1</sup> )	0.00973 ± 0.00103		
Cl1 (mL/min/kg)	65.1 ± 2.3		
Cl2 (mL/min/kg)	104 ± 11		
Cl1_F (mL/min/kg)		318 ± 33	240 ± 45
V1 (mL/kg)	2340 ± 270		
V2 (mL/kg)	10700 ± 800		
V1_F (mL/kg)		78100 ± 11900	46400 ± 12300
MRT (minute)	200 ± 11		
AUC_0-T (ng mL <sup>-1</sup> min)		83400 ± .	159000 ± .
AUCinf_pred (ng*mL <sup>-1</sup> *min)	24600 ± 900	78700 ± 8200	208000 ± 39000

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**Female**

**Treatment Group (mg/kg)**

**1.6 IV Plasma<sup>d</sup>**

**25 Gavage Plasma<sup>b,e</sup>**

**50 Gavage Plasma<sup>c,e</sup>**

C_0min_pred (ng/mL)	522 ± 99		
Cmax_pred (ng/mL)		440 ± 110	2270 ± 450
Tmax_pred (minute)		8.31 ± 8.37	18.4 ± 7.0
Cmax_obs (ng/g)		613 ± 532	2630 ± 2180
Tmax_obs (minute)		5.00 ± 0.00	30.0 ± 0.0
k01 (minute <sup>-1</sup> )		0.584 ± 0.747	0.183 ± 0.098
k01 Half-life		1.19 ± 1.51	3.78 ± 2.02
k10 (minute <sup>-1</sup> )	0.0807 ± 0.0109	0.00472 ± 0.00113	0.00723 ± 0.00069
k10 Half-life (minute)	8.59 ± 1.15	147 ± 35	95.9 ± 9.1
k12 (minute <sup>-1</sup> )	0.0241 ± 0.0051		
k21 (minute <sup>-1</sup> )	0.0165 ± 0.0036		
Cl1 (mL/min/kg)	248 ± 20		
Cl2 (mL/min/kg)	73.8 ± 14.1		
Cl1_F (mL/min/kg)		258 ± 56	140 ± 25
V1 (mL/kg)	3070 ± 580		
V2 (mL/kg)	4470 ± 1060		
V1_F (mL/kg)		54600 ± 14900	19300 ± 4500
MRT (minute)	30.4 ± 4.7		
AUC_0-T (ng mL <sup>-1</sup> min)		77300	307000
AUCinf_pred (ng*mL <sup>-1</sup> *min)	6460 ± 250	97100 ± 21100	358000 ± 64000

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**Male**

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**Treatment Group (mg/kg)**

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**1.6 IV Brain<sup>a</sup>**

**25 Gavage Brain<sup>a</sup>**

**50 Gavage Brain<sup>a</sup>**

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Cmax_obs (ng/g)	1590 ± 520	728 ± 38	1720 ± 660
Tmax_obs (minute)	10.7	15.3	16.7
Half-life (minute)	60.0	107	86.1
AUC_0-T (ng*g <sup>-1</sup> *min)	67900		
AUC_0-T (ng/g*min)		81400	249000
AUCinf_pred (ng*g <sup>-1</sup> *min)	68600		
AUCinf_pred (ng/g*min)		91000	266000

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**Female**

**Treatment Group (mg/kg)**

**1.6 IV Brain<sup>a</sup>**

**25 Gavage Brain<sup>a</sup>**

**50 Gavage Brain<sup>a</sup>**

Cmax_obs (ng/g)	1810 ± 360	2330 ± 1450	5820 ± 1100
Tmax_obs (minute)	8.67	14.7	15.7
Half-life (minute)	43.7	206	149
AUC_0-T (ng*g <sup>-1</sup> *min)	45400		
AUC_0-T (ng/g*min)		224000	658000
AUCinf_pred (ng*g <sup>-1</sup> *min)	46000		
AUCinf_pred (ng/g*min)		306000	673000

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## LEGEND

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### MODELING SOFTWARE

WinNonlin Version 5.0.1

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Noncompartmental Analysis (NCA)

<sup>b</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, one-compartment with first order absorption and elimination with 1/Y<sup>2</sup> weighting (Model No. 3)

<sup>c</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two compartment with first order absorption and elimination with 1/Y weighting (Model No. 13)

<sup>d</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, One compartment with bolus input and first order elimination with 1/Y<sup>2</sup> weighting (Model No. 1)

### EXCEPTION

<sup>e</sup> AUC 0-T standard error of the mean, SE, was ND, not detected.

### ANALYTE

Alpha-Thujone

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#### TK PARAMETERS

C\_0min\_pred = Fitted plasma concentration at time zero (IV only)

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax = Time at which Cmax predicted or observed occurs

Half-Life =  $\lambda_z$  Half life,  $t_{1/2}$ , the terminal elimination half-life based on non-compartmental analysis

Alpha Half-Life = Half-life for the alpha phase

Beta Half-Life = Half-life for the beta phase

k01 = Absorption rate constant,  $k_a$

k01 Half-life = Half-life of the absorption process to the central compartment

k10 = Elimination rate constant from the central compartment also  $k_e$  or  $k_{elim}$

k10 Half-life = Half-life for the elimination process from the central compartment

k12 = Distribution rate constant from first to second compartment

k21 = Distribution rate constant from second to first compartment

Cl1 = Clearance of central compartment,  $Cl_{app}$  or apparent clearance for intravenous groups

Cl2 = Clearance of the secondary compartment

Cl1\_F = Apparent clearance of the central compartment, also  $Cl_F$  for gavage groups in non-compartmental model

V1 = Volume of distribution of the central compartment, includes  $V_d$  and  $V$  volume of distribution,  $V_z$  apparent volume of distribution NCA,

$V_{app}$  apparent volume of distribution for intravenous studies

V2 = Volume of distribution for the peripheral compartment

V1\_F = Apparent volume of distribution for the central compartment includes  $V_{d,F}$ ,  $V_F$  for oral groups, and  $V_{c,F}$

MRT = Mean Residence Time

AUC\_0-T = Area under the plasma concentration versus time curve, AUC, from time  $t_i$  (initial) to  $t_f$  (final), AUClast

AUCinf\_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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## TK PARAMETERS PROTOCOL

### ANALYSIS METHOD

Target times for blood and brain collection for the intravenous phase of the study were - male rats at 5, 10, 20, and 45 minutes, and 1, 2, 4, 6, 8, and 12 hours; female rats at 5, 10, 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, and 3 hours; and male and female mice at 2, 5, 7, 10, 15, 20, 30, and 45 minutes, and 1 and 1.5 hours. Target times for blood and brain collection for the gavage phase of the study were: male and female rats at 2, 5, 10, and 30 minutes, and 1.5, 3, 6, and 12 hours; and male and female mice at 2, 5, 10, 20, and 40 minutes, and 1.5 hours, 2 hours (40 mg/kg female mice only), 3 hours, 4 hours (80 mg/kg female mice only), 5 hours (40 mg/kg male mice only), and 6 hours (80 mg/kg male mice only).

### TK\_INTRAVENTOUS PLASMA

#### 1.6 mg/kg Male and Female

Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 7/1-3/02.

### TK\_GAVAGE PLASMA

#### 25 mg/kg, 50 mg/kg Male and Female

Twenty-four animals/species/sex/compound/dosage group (excluding replacements) were given a single oral gavage administration of a-thujone or a,b-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/17-20/02.

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#### TK PARAMETERS PROTOCOL (cont'd)

##### TK\_INTRAVENTOUS BRAIN

###### 1.6 mg/kg Male and Female

Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 7/1-3/02.

##### TK\_GAVAGE BRAIN

###### 25 mg/kg, 50 mg/kg Male and Female

Twenty-four animals/species/sex/compound/dosage group (excluding replacements) were given a single oral gavage administration of a-thujone or a,b-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/17-20/02.